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THE THERAPEUTICS OF THE INTERNAL SECRETIONS.*

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THE various theories which have been deduced from experimental, pathological, and clinical observations of the functions of the ductless glands, together with a review of the results of therapeusis in their various diseases, based upon such theories, will be presented in this paper.

Although it has long been surmised that the secretions of the ductless glands were of vital importance to the bodily economy, it is only lately that they have been shown to rival in their *rôle* the part played in metabolism by the glands provided with ducts, such as the liver and pancreas.

The Thyroid Gland. Experimental, pathological, and clinical investigations have demonstrated the vital importance to the economy of the physiological function of the thyroid gland. Defective development, pathological changes, destructive or otherwise, and experimental removal, induce a train of well-known symptoms which necessitate the acceptance of one of two theories as to the nature of its function:

1. That its office is chiefly, if not wholly, a secretory one; that it furnishes some material which enters the blood, probably through the lymphatics, and which is essential for the chemistry of metabolism and for the proper nutrition of the various tissues.

2. That its function is to neutralize or destroy certain poisons which

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result from tissue-changes, and which, by their tendency to accumulate in the blood, induce autointoxication.

The arguments, and they are many, which may be advanced in favor of either one of these theories, will be more properly considered in the papers devoted to the physiological and pathological aspects of the subject. Experimental and clinical observations have demonstrated that the *specific* function of the gland, whether it be to aid metabolism or to develop an antitoxin, can be replaced by a suitable dosage of extracts or preparations of the normal gland administered subcutaneously or by the digestive tract. If the specific purpose of the gland is antitoxic, it is thus evident that this function can be effectively exercised in the blood-current or tissues, even if normally it is partly or chiefly effected within the gland-substance.

In diseases, therefore, which have been shown to be due to a loss of function of the thyroid gland, myxœdema, cretinism, both sporadic and endemic, and operative myxœdema (cachexia strumipriva) the indication for treatment is direct, and the results are among the most brilliant examples of the value of a therapeusis which is based upon experimental pathology.

The number of cases of myxœdema treated with the thyroid preparations is already very great, and experience justifies the formulation of many practical rules in this method of therapeusis. The most important of these rules were to be inferred from the pathology of the disease. Although the myxœdematous symptoms are speedily removed by the treatment, a discontinuance of the treatment is certainly followed by a return of the myxœdema at varying intervals, showing that the treatment does not cause the gland to resume its function, but exercises its influence by introducing into the economy something which it is presumably the function of the gland to supply. It has been shown conclusively, first, that complete recovery can be effected even after the disease has existed for as long a period as fourteen years and in the case of patients bed-ridden and presenting the gravest symptoms ; and, secondly, that the maintenance of health can only be secured by continuous treatment during the lifetime of the patient. The requisite dosage after the removal of the myxœdematous condition has been found to vary, and depends upon the degree of loss of glandular function. Equally good results are obtained from a single daily dose or a larger dose given at longer intervals. It has been found that this interval rarely can exceed a week.

The complete restoration of physical strength, aside from the general well-being of the patient, is well illustrated in a case of Murray's,[1] a male, who from being practically disabled, at the end of two years after the beginning of treatment was able to make the ascent of a mountain 3000 feet high, including a walk of ten miles, without any undue fatigue.

It may be of interest to refer to the subsequent history of a woman, forty-three years of age, under my personal care, who was among the first to be treated by thyroid preparations in this country (1892). The disease had existed for twelve years; she had been bed-ridden for a year; she had lost her hearing, was hairless, and suffered from marked mental hebetude and grave physical prostration. After the marvellous improvement usually effected in the first few weeks of treatment she continued to improve, and for the past two years she has admirably filled a responsible librarian's position in addition to performing easily all the duties of the head of a household. Her hearing is perfect; she has a new growth of hair of the finest fibre reaching to her waist, and the brilliant coloring and texture of skin rarely seen except in youth. She maintains her present condition of health by taking the equivalent of five grains of the fresh sheep's thyroid twice weekly.

Cretinism, sporadic and endemic. Continued experience during the few years which have elapsed since the treatment of cretinism with thyroid preparations was first instituted has confirmed the hopes which were originally entertained of its efficacy. It has been shown conclusively, first, that in sporadic cretinism the myxœdematous symptoms can speedily be removed, thereby effecting a marvellous improvement in the frightful deformities incident to the disease; secondly, that the treatment is capable of developing the natural tendencies of the growth of the skeleton which were in abeyance, and that this latent capacity is in apparent inverse ratio to the age of the patient; thirdly, that a striking improvement in the mental condition is effected, although occurring more slowly and in a similar inverse ratio to the age of the patient, as observed in the skeletal growth. The rate and degree of the growth of the skeleton at different ages are strikingly illustrated in the cases of cretinism reported by Thomson[2] at the last meeting of the British Medical Association. In the case of a child, five years of age, who was seven inches below the normal height at the beginning of treatment, the growth was five and three-quarters inches in the first year of treatment, four and one-quarter inches in the second year, and two and one-half inches in the third year. In a girl of eighteen years the growth was four and three-quarters, two and three-eighths, and one and three-eighths inches in the first, second, and third years respectively. And, finally, in two adult cretins, thirty-six and thirty-nine years of age, the growth in one was three-quarters of an inch and five-eighths of an inch in the first and second years, and none in the third; in the other, one and seven-eighths and three-quarters of an inch represented the growth in the first and second years, and there was no further growth in the third. These results are very similar to those reported by many other observers.

The radiograph has been utilized by Hertoghe for purposes of prognosis in cases of this kind. The completeness or incompleteness of ossification, demonstrable in this way, indicates the possibility of further skeletal growth.[3]

An interesting point in the skeletal growth is that, as the child approaches the height normal at a definite age, continuous growth apparently is only at the usual rate. In the very rapid growth of the bones a tendency to softening, resembling that which occurs in rickets, has been noted by several observers, and has been ascribed to the use of doses of the thyroid extracts which were probably too large. It is, perhaps, too soon to speak positively of the degree of mental improvement attainable; but already cases of cretinism in children have been reported where the intelligence after three years of treatment has compared favorably with that of normal children of a similar age.

In view of the facts related it is not unjustifiable to conclude that the treatment of cretinism with the thyroid preparations, if initiated early in the disease and systematically continued, holds out every promise of the child's development into a healthy adult.

The therapeutic value of thyroid preparations in cretinism has suggested their use in cases of idiocy more or less resembling in bodily and mental defects the cretinous condition.

Bourneville has shown that the weight of the thyroid gland varies very considerably in different cases of idiocy.

Telford Smith[4] has tried the treatment in idiots belonging to the Mongol type, who most closely resemble the cretin. His experience has been that a physical and mental improvement occurs, and that it is inversely to the age of the patient; that the improvement is neither so rapid nor so marked as in the cretin. There is some improvement in the condition of the skin; it desquamates, but does not become normally smooth; chronic marginal blepharitis improves and in some cases is cured. Growth improves as well as the mental condition.

Goitre. Turning from a consideration of the thyroid treatment in pathological conditions necessarily involving a loss of function of the thyroid gland to other morbid conditions in which its function may be variously affected, goitre first attracts our attention.

The benefit derived from the use of the thyroid preparations in cases of goitre in which the absence of constitutional symptoms indicates that the function of the thyroid gland is still largely preserved, has not been satisfactorily explained. The benefit consists in a retrogression of the goitre through atrophy of the hyperplastic and adenomatous tissues.

The maximum improvement is obtained in goitre of the simple hyperplastic form, although adenomatous nodules in many instances shrink in a striking manner. Large collections of colloid and cysts are apparently unaffected by the treatment. The diminution in the size of colloid goitres Kocher attributes to a shrinking of the parenchymatous tissue in which the colloid is imbedded. Although marked diminution in size in the varieties of goitre which have been mentioned, and a corresponding improvement in the patient's general condition, occur, complete disappearance of the tumor has rarely been noted. The reports of various observers of the permanent improvement or cure are not sufficiently full to justify positive statements on these points at the present date. Recurrence of the tumor after partial or complete disappearance, at varying intervals after the discontinuance of the treatment, certainly occurs in many instances, and suggests the possibility that continued use of the thyroid preparations in a modified way for indefinite periods may be found necessary.

Bruns has reported 60 cases,[5] non-malignant and non-cystic in character, treated by this method; 14 were cured, 29 were improved, and 17 were not benefited by the treatment.

In 21 cases reported by Knoepfelmacher,[6] in 11, the patients varying from two to seventeen years of age, the retrogression of the goitre was marked, although in none was it completely removed; of these, 9 cases were of the hyperplastic type. In 5 other cases of colloid goitre a perceptible diminution in the size of the tumor was effected. In the remaining 5 cases no improvement was observed.

Angerer[7] has treated seventy-eight cases with thyroid preparations, and claims that in all the cases in which the treatment was tolerated and continued for a period of several weeks diminution in the size of the goitre was attained. The most striking results were noticed in the soft goitres of the simple hyperplastic form, and especially in those occurring about the age of puberty. In cystic goitres, through the atrophy of the hyperplastic tissues, the cysts became more superficial, and their enucleation was thereby rendered more simple.

In eighty-three cases of Stabel's improvement was obtained in 92 per cent. In only two was there unquestionably permanent recovery. Stabel[8] states that after the administration of thyroid substance was discontinued the tumor, in cases in which it had decreased, again began to increase in size at varying intervals of four to six weeks.

In explanation of the action of thyroid gland preparations in goitre, Bruns, Ewald, and others have suggested the hypothesis of a primary toxæmia of unknown origin, which evokes an increased functional activity of the gland, accompanied by hypertrophy. If the demand for thyroid products is supplied artificially, the gland retrogrades and atrophy results.*

Exophthalmic Goitre. *A priori*, benefit would not be expected from the thyroid preparations in exophthalmic goitre, as increased functional activity of the thyroid gland probably occurs in this disease, and the preponderance of evidence indicates that their use is commonly attended with an aggravation of the symptoms.

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* Bauman's isolation of an iodine-bearing compound (iodothyrine) from the thyroid gland secretion suggests an explanation of the value of iodine in the internal treatment of goitre.

In certain cases, however, the employment of thyroid extracts is unattended with any appreciable effect. The natural fluctuations of the disease, improvement alternating with recrudescences, suggest that the exceptional reports of *improvement* under this treatment have been based upon insufficient grounds.

Finally, the thyroid treatment has been employed in various pathological conditions in which a perversion of the function of the thyroid gland has yet to be proved.

Without such perversion it is probable, from the power of the active principle to quicken metabolic processes, that the treatment would be of value.

Insanity. The use of thyroid preparations in the treatment of various forms of insanity was originally based upon its undoubted power to increase ultimate cell-metabolism.

A relatively large number of cases treated by this method have been published. Bruce[9] has reported 60 cases, 25 males whose ages ranged from twenty to fifty-five years, and 35 females whose ages ranged from twenty to fifty years. Of the males 7 recovered under treatment, and there were 17 recoveries among the females. Thirteen of these latter were either puerperal, lactational, or climacteric cases.

Bruce believes that the action of thyroid in insanity is a complex one:

1. That the feverish condition induced by it is of benefit to the patient.
2. That it acts as a direct cerebral stimulant.
3. That it supplies some material necessary to the economy which the gland is supplying in insufficient quantity.

Babcock has published twenty-two cases treated in the St. Lawrence State Hospital for the Insane.[10] In four cases there was recovery; in eleven, improvement. The four recoveries were in patients suffering from recurrent mania and melancholia. Improvement was obtained in cases of acute mania and acute melancholia, in two cases of acute delirium, in a case of chronic mania, and in one of chronic melancholia. Relapses occurred in four cases. In one of these (chronic melancholia) relapses followed two successive treatments.

Allen Starr's[11] extensive experience has led him to place the highest value upon the treatment* in a form of mental disturbance occurring at the climacteric. He describes it as a mental depression with anxiety and morbid fears, but without delusions or insomnia. Starr is inclined to believe that a functional disturbance of the thyroid and ovaries is associated in these cases.

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* Clouston says "that large doses of thyroid are of marked benefit in cases which threaten to become chronic, and that no case should be allowed to become incurable without a trial of this method of treatment."

These results correspond closely with those obtained by various other observers and indicate a decided advance in the therapeusis of certain forms of insanity. The favorable or unfavorable response to the treatment is even accepted by several distinguished alienists as affording a basis for prognosis in the large class of cases occupying "the borderland" between curable and incurable states.

Obesity. The literature of the thyroid treatment of obesity is already very voluminous. The number of published cases treated by this method during the past four years is large, and the results in general have been favorable.

The researches of Treupel, Grawitz, Roos,[12] and Hennig, among others, have shown that under the influence of the active principle there is a decided increase in the excretion of nitrogen as compared with the amount received in the diet.

In the discussion in the Fourteenth Congress for Internal Medicine Ewald stated that the thyroid preparations influenced metabolism *in toto*, without a selective action on the fats, and hence that there was an albuminoid waste which should be compensated for by an appropriate diet. In certain cases he had found the treatment to be without effect, an experience which harmonizes with that of other observers, and that its failure was observed not only in the class of patients which accumulated fat in spite of a careful dietary, but also where the obesity is the result of excessive indulgence. In such cases the fatty deposits lie beyond the limit of the control of the oxidation processes.

In patients who react to treatment the loss of weight varies from 1 to 5 kilogrammes (2 to 11 pounds) a week, without restriction of diet, but after a time a limit is reached beyond which further reduction is not obtained. The loss of weight is more rapid during the first days of treatment than later; subsequently it varies in amount from week to week, without explainable reason, the conditions of life remaining the same. The loss is usually unattended with any disturbance of health. As a rule, the discontinuance of treatment is quickly followed by an increase of weight, which shortly reaches its former level. Only exceptionally is the improvement maintained for any considerable period, although careful dieting and exercise prolong its duration.

Cutaneous Diseases. The expectations originally entertained of the value of thyroid treatment in diseases of the skin have not been fulfilled. Only in psoriasis has some small measure of success been obtained. Even in this disease the effects are uncertain; it is impossible to differentiate the type of the affection in which benefit may be expected, and in many cases an aggravation of the lesions occurs.

Phthisis. The suggestion of the possible value of thyroid preparations in phthisis rests on the slender basis of their temporary effects in some cases of lupus, upon the assumed antagonism of goitre and tuberculosis, and finally upon the atrophy of the thyroid gland in chronic, wasting diseases. Morin[13] and Kraus claim favorable results from their use.

As early as 1893 the treatment was instituted in my hospital wards in carefully selected cases of pulmonary tuberculosis, and the conclusions reached were that it was absolutely without effect either upon the lesions or the general condition of the patient.

The use of thyroid preparations has been further extended, and claims of their therapeutic value in various other morbid conditions have been made.

Further careful investigation and corroboration are demanded before they can be finally accepted.

Attempts have been made by various investigators to isolate the specific principles of the thyroid. Exclusive of Fränkel's discovery of a substance of active properties, but which does not prevent the occurrence of the chronic cachexia, Baumann has isolated an iodine-bearing compound of albumin and globulin, which he has named " Iodothyrine."[14] He believes it to represent the total specific activity of the glandular extract, which he makes dependent upon the amount of iodine it contains.

R. Hutchinson[15] has within the last few months published the results of his investigations into the active principles of the thyroid, which in the main corroborate those of Baumann. He finds that the thyroid contains two proteids, viz., a nucleo-albumin and a colloid matter; the former is small, the latter large in amount. The colloid contains a small amount of phosphorus and a considerable proportion of iodine. On gastric digestion it splits up into a non-proteid and a proteid portion, both of which contain iodine, but chiefly the non-proteid portion.

The colloid matter is the only active constituent of the gland in a specific sense. Both the non-proteid and the proteid portions of the colloid are active, but the former (apparently identical with Baumann's iodothyrine) is much more so than the latter.

The Adrenals. With the exception of Tizzoni's[16] notable experimental investigations, from which he concludes that the adrenals are functionless and derive their importance from their anatomical relation to the sympathetic, all modern work strongly indicates that they are functionally active glands.

The theories advanced in regard to the nature of their function are:

1. That their office is to neutralize or destroy certain toxins and effete blood-pigments which are constantly accumulating in the blood; that their function is excretory.

2. That their function is a secretory one; that they elaborate some

substance which enters the circulation and which is necessary to the economy.

Excretory theory. The excretory theory is based largely upon the apparent toxicity of the blood of animals deprived of their adrenals;[17] upon the respective effects of injections, into the peritoneal cavities of rabbits, of solutions of nicotine which had been kept in contact for varying periods with fresh adrenal tissue, and solutions of nicotine of the same strength with or without contact with muscular or renal tissue (Charrin and Langlois[18]); upon the effects of atropine upon completely acapsulated animals (Abelous[19]); and finally upon the results obtained in guinea-pigs, normal and monacapsulated, by the injections of both sterilized and virulent cultures of the bacillus pyocyaneus (Langlois and Charrin[20]).

The conclusions of these observers are that the functions of the adrenals are to produce one or more substances designed to neutralize or destroy the toxins normally arising from muscular metabolism, and, perhaps, also certain poisons accidentally introduced from without, including those of bacterial origin.

Secretory theory. The secretory theory is based upon the physiological effects obtained experimentally by subcutaneous and intravenous injections of extracts of the adrenals.

Cybulski,[21] from an extended series of experiments, concludes that the adrenals furnish an indispensable secretion which diffuses continuously from the glandular parenchyma, more especially of the medullary substance, into the blood-current, its office being to maintain the activity of the vasomotor centres, the vagi and accelerator nerves, the respiratory centre, and with great probability, also, the centre which maintains muscular tonus.

He claims that the active principle can be extracted by alcohol or glycerin and a variety of other solvents, that it is not destroyed by boiling, and will dialize. If the gland is boiled previous to extraction, it will not yield its active substance to water; or if it be dried at a temperature of 110° C., the alcoholic extract is inert and the watery very much weakened. When introduced into the veins of an animal it causes a marked but very brief increase in blood-pressure and a slowing and increase in force of the heart-action, with diminished respiratory efforts. This effect is never obtained from similar preparations from the brain, spinal ganglia, lymph-glands, liver, spleen, kidney, testicle, or thyroid of the calf and ox.

By an independent series of investigations Schaefer and Oliver[22] have arrived at essentially the same results. Aside from some disagreement in a few particulars relating to the method of extraction and chemical peculiarities of the active agent, they differ from Cybulski chiefly in holding that the action is exercised directly upon the muscles, and not through the intervention of the nervous system. They reject the theory that the brief effect and rapid disappearance are due to oxidation, and suggest that the substance may be stored up in the skeletal muscles, and lay particular stress upon the exceedingly minute dosage which suffices to produce the vascular phenomena which they found so prominent.

They agree with Cybulski in localizing the active principle to the medullary portion of the gland.

They conclude from their investigations that the suprarenal capsules are secreting glands which elaborate a material producing striking physiological effects upon the muscular tissue generally, and especially upon the heart and arteries, and that, therefore, one of the main functions, if not the *main* function, is to produce a material which is added in some way or another to the blood, the effect of which is to assist, by its direct action upon the various kinds of muscular tissue, in maintaining that amount of tonic contraction which appears to be essential to the physiological activity of the tissue.

Some very recent work indicates the presence in the adrenals of more than one active principle, and two theories attract our attention :

Mühlmann[32] believes that he has demonstrated the presence of a combination of pyrocatechin in the medullary substance. According to his hypothesis, it is one of the functions of the suprarenal capsules to convert the protocatechuic acid derived from the vegetable elements of diet into pyrocatechin. The latter substance in small doses elevates blood-pressure, while in larger doses it is toxic. The herbivora are less sensitive to its influence, probably as an effect of habituation. Its elimination or conversion into harmless products is believed to be accomplished through the intervention of some unknown activity of the ganglion-cells of the sympathetic. If the latter function fail or the pyrocatechin be produced in excess, toxic symptoms arise, accompanied by an abnormal pigmentation derived from the reaction between the tissues and this substance in the presence of alkalies. The author does not exclude the presence of other active principles and other functions of the gland, but considers his hypothesis to afford the best explanation of the toxic effect of adrenal extracts and the occurrence of pigmentation of adrenal origin.

Gourfein[24] and subsequently Dubois[25] have endeavored to isolate the various active principles obtainable from the suprarenal gland.

Without entering into the complex details of their chemical experiments, it is sufficient to state that Dubois has separated the active principles into two classes. The first is composed of several albumoses which may be precipitated with alcohol and redissolved in water. The substances so isolated have no well-marked toxic effect, but they and they alone seem to possess therapeutic importance, manifested by their influence in diminishing or even preventing the results of the injection of muscle-toxins. He regards these antitoxins as diastases or substances endowed with an inherent dynamic activity which cannot be isolated from the protoplasmic bodies with which it is associated. The second class is composed of bodies which resemble in their constitution and reactions the alkaloids. They have a marked degree of toxic effect, and are identical in some of their reactions with the muscle-toxins. This leads the author to favor the theory that the suprarenal bodies, like the liver, occlude the products of organic waste and modify them *in loco* by the action of special diastases.

Dubois concludes that the chief function of the suprarenal capsules is to destroy the toxins in circulation, especially those resulting from muscular waste and perhaps those furnished by the nervous tissue ; that they do not seem to secrete any special substance destined to enter the general circulation, but that their cellular protoplasm possesses a special diastatic property, non-toxic, which seems to modify certain poisons, organic and bacterial, yet this action requires time, and proceeds little by little ; that in normal conditions there are always alkaloids present, especially in the medullary zone, which possess an intense toxic action upon both striped and unstriped muscular fibre, and upon certain nervous elements not yet fully defined ; that it is the retention of these excrementitious products which brings about serious symptoms ; that their quantity may vary under the influence of numerous conditions ; and that no positive therapeutic results can be obtained until we are able to separate definitely and completely the toxic and the antitoxic principles which coexist in the suprarenal capsules, as glycogen and its ferment coexist in the liver.

On the basis that the adrenals are functionally active, the employment of adrenal preparations has been advocated in pathological conditions necessarily attended with loss of function of these glands.

I have been able to collect forty-eight cases of Addison's disease treated with various adrenal preparations. They have been tabulated with brief notes of their salient points. Six patients are reported as cured or practically well, 22 improved, 18 unimproved, and in 2 instances an aggravation of the symptoms is stated to have occurred during treatment.

Among the six recoveries, in one instance the patient has remained well for four months ; in a second case the treatment was continued for four and one-half months, the pigmentation disappeared, and the patient was able to return to work. He is still under observation one year and a half after the treatment was instituted, and is still well. In a third case the patient was practically well at the date of the last report, twelve months after the beginning of treatment.

In the cases in which improvement was noted relapse and death occurred in one ; in another the improvement was only temporary, death following ; in a third case, the treatment was irregular, and the patient was relapsing at the date of the last report. In a fourth case improvement in the asthenia and pigmentation was observed until the end of the fourth week, when, the appetite failing, treatment was suspended, and death occurred two weeks later. In another patient there was marked improvement during regular treatment. During the subsequent months the treatment was irregularly pursued, and eight months later the patient was reported as failing rapidly. In Bramwell's case there was remarkable improvement for a year, the patient being able to resume his ordinary occupation, when death occurred. In still another case improvement had been maintained for twenty months at the date of last report. The patient had been able to return to work, but relapses occurred when the treatment was suspended. Finally, in one case there was improvement for three months, when the patient died quite suddenly on the discontinuance of the treatment.

In many of the cases related the association of adrenal disease with grave tuberculous lesions elsewhere in the body precluded the possibility of obtaining more than an amelioration of symptoms; nevertheless, the results secured justify the hope that perhaps with the isolation and differentiation of the several active principles, if several there be, of the glandular structures, an efficient therapeusis may be obtained for the simple atrophies and fibroid degenerations of the adrenals, which it has been demonstrated may be both localized and provocative of some of the phenomena of so-called Addison's disease.

The rise of blood-pressure produced by the active principle of the adrenals, through its action either directly or indirectly upon the muscular walls of the bloodvessels and the heart-muscle, has suggested the possible therapeutic value of the adrenal preparations in pathological conditions other than those necessarily attended with loss of function of the gland.

Where the vasomotor tone is lowered, as in asthenia and anæmia, their use would seem to be indicated, and Oliver[26] claims benefit has been noted. In cyclic albuminuria he also states that he has obtained good results from their employment. Oliver also suggests their probable value in heart-failure, as there seems to be some resemblance between the physiological action of the active principle and that of digitalis. In a few cases of this kind adrenal extract has very recently been tried in my hospital wards, and with apparent benefit. The rapid rise in blood-pressure was distinctly shown by the sphygmograph, and was also appreciable to the finger. Further study is necessary to determine their true therapeutic value in the conditions mentioned.

Schaefer and Oliver's investigations indicate that the active principle is not unfavorably influenced by gastric digestion; hence that the various preparations properly may be administered by the mouth, and again, that comparatively large doses may be given to man with safety. A daily dosage equivalent to 45 grains of the fresh gland is recommended for therapeutic use. It can be given continuously for very long periods without injurious effect.

Thymus Gland. The determination of the true physiological position of the thymus gland in the human economy is especially difficult on account of the several histological phases in its natural history.

Closely related to the thyroid gland in its manner of origin, the structure of glandular epithelium of the first four months of intrauterine life gradually gives place to a lymphadenoid structure which reaches its maximum development at birth. This lymphadenoid thymus is normally present until the period of puberty, when it is gradually replaced by the lobulated fatty thymus, which persists indefinitely in man.

It would, therefore, seem that the existence of a secretory function is presumable only in the first months of intrauterine life. Whether the function of the lymphadenoid thymus differs from that of other lymphadenoid structures yet remains to be determined. The discovery by Baumann of minute amounts of an iodine-bearing compound in its tissues,[27] a substance not found in other organs, with the exception of the thyroid gland, is suggestive.

It is thus evident that the physiological basis for the therapeutic use of thymus gland is a slender one.

Clinically, the original employment was accidental, and explanations of its action at present must be regarded as largely speculative.

Owen's published case of exophthalmic goitre,[28] in which benefit was observed from feeding with thymus gland which had been used by mistake for thyroid, introduced the thymus treatment of this disease.

I have collected 62 cases of exophthalmic goitre treated by this method. In 36 cases improvement of varying degree occurred; in 25 there was no improvement, and in 1 there was an aggravation of symptoms, resembling in all respects that commonly caused by thyroid feeding in this disease. In one of the unimproved cases a combination of thymus and thyroid was employed at first, and later the thymus alone was given until a few days before death.

In the cases of improvement the effect upon the more characteristic symptoms was as follows:

Exophthalmos: the exophthalmos disappeared in 8 cases; in 1 it nearly disappeared; in 8 it was diminished in amount; in 1 it is stated that the patient was practically cured; in 6 the symptom is not mentioned; and in 12 there was no effect.

Goitre: in 4 cases a slight enlargement of the thyroid gland disappeared; in 12 the size was reduced; in 13 there was no effect; in 7 the goitre is not mentioned.

Pulse-rate: in 17 cases the pulse-rate was reduced; in 3 of these the reduction was very slight. In 13 cases there was no diminution in the frequency of the pulse; in 6 cases the symptom is not mentioned.

In a large proportion of the 36 cases it is evident that there was an improvement in the subjective sensations, and in many in the general condition, including a gain in weight. In the remaining 26 of the 62 cases either no beneficial effect was observed or an aggravation of symptoms occurred.

It is desirable to compare the favorable results which have been described with those obtained by other methods of treatment.

McKenzie[29] has carefully contrasted twenty cases of exophthalmic goitre personally treated by him with thymus preparations, either alone or combined with other remedies, with a similar number also personally treated by other methods. As regards the pulse-rate, " there was nothing in favor of the thymus treatment." The goitre became materially smaller in three cases under thymus treatment; in two it increased, and in another it increased after first diminishing. In the remaining cases it remained practically unchanged.

In the *contrast*-cases the goitre diminished in four; in a fifth it entirely disappeared; in one case it increased; in the remainder no change was observed. Under the *thymus* treatment proptosis decreased distinctly in only one case, and in this instance a reduction had begun before the thymus was given. In the *contrast*-cases the exophthalmos disappeared in three.

McKenzie's conclusions are that the thymus gland possesses no specific action in exophthalmic goitre; that " in most cases it has no effect upon the heart, goitre, or proptosis." At the same time he believes it to be " a remedy of some value, improving the general condition, and in this way assisting toward recovery." He places it in the same class of remedies as cod-liver oil.

In two severe cases carefully observed from day to day in my hospital wards for the past five months, in which the thymus treatment alone was used for two months, and other methods subsequently, the former treatment was without the slightest beneficial effect upon any symptom. In one the thyroid increased by an inch during the thymus period. In contrast, in one of these cases there was marked improvement in the tremor, a diminution in the pulse-rate, a reduction in the goitre of an inch, with improvement in the general condition, accompanying the use of bromides and belladonna, to be followed again by a recrudescence of the symptoms.

Maude,[30] in reporting four cases treated with marked benefit with thymus preparations, remarks that he " cannot claim that the rapidity and maintenance of improvement have been more than might occur under other treatment, or none at all."

In judging of the therapeutic value of the thymus treatment in exophthalmic goitre too much reliance should not be placed upon the relative number of published cases of successes and failures. Favorable results from a new remedy are more frequently reported than failures.

Finally, in few diseases is it as difficult to speak positively of the value of any particular method of treatment. The natural fluctuations of the disease are great, and improvement and recrudescence occur often in an unexplainable manner.

Goitre. Mikulicz[31] has reported thirty cases of goitre treated with thymus extracts. In twenty cases the goitre underwent a decided reduction, as ascertained by exact measurements, and subjective improvement followed. Among these are several cases which had only slightly improved or which had become worse under thyroid treatment. A complete cure in the anatomical sense was only obtained in two cases. With the exception of one case (mixed nodular and diffuse parenchymatous) they were all diffuse hyperplastic tumors. Five of the unsuccessful cases were of the nodular, and five of the diffuse hyperplastic form.

The mode of action of the remedy remains a matter of speculation. It is possible that the active principle is an iodine compound, which Baumann was able to isolate in the case of the thymus as well as the thyroid gland.

In view of the possible stimulation of the nutritive processes in exophthalmic goitre by the thymus extracts, it is of interest to study their effects in other diseases attended with impaired nutrition.

With this object in view the treatment was tried in my hospital wards during the past winter in six carefully selected cases of apyretic pulmonary phthisis.

The general condition, weight, and physical signs of the patients were carefully noted for a period before the institution of the thymus treatment. The extract in daily doses of 45 grains, speedily increased to a drachm, was then given continuously for two months, when the usual treatment of the hospital—creosote, the malt preparations, and cod-liver oil—was resumed.

In Case I. (infiltration of one apex) the weight, which had been nearly stationary, increased two pounds during the first three weeks of treatment; there was a loss of six pounds during the subsequent five weeks, when the usual treatment was resumed.

In Cases II. and III. (consolidation at one and at both apices respectively) the weight was stationary prior to treatment. There was a gain of four pounds in each case during the first three weeks, and then a loss of eight pounds in one case and two pounds in the second case in the subsequent five weeks. In the following two months, under ordinary treatment, in the case showing the greatest loss, there was a gain of two pounds; in the other there was no gain.

In Case IV. (consolidation at both apices) there was a gain of two and one-half pounds in the first two months, and then a loss of three and one-half pounds in the succeeding two months under other treatment.

In Case V. (infiltration at one apex) a gain of seven pounds in three weeks was followed by a loss of four in the succeeding five weeks, which was again followed by a gain of two pounds in the seven weeks subsequent to the discontinuance of the thymus.

Finally, in Case VI. (consolidation at both apices) there was a gain of a pound in the first week, and a continuous loss, amounting to eight pounds, from this time until other treatment was substituted for the thymus. In five of the six cases it is seen that an increase in weight occurred during the first weeks of treatment. The gain was followed by a loss, varying in amount. In only one case was there no loss in weight during the two months of the thymus treatment.

In all the cases there was little or no change in the general condition and physical signs during the thymus treatment, although at first, as is so often the case with the trial of a new remedy with the knowledge of the patient, expression of improvement in subjective sensations was made.

Whether the favorable response in the first weeks to the remedy, as shown in improved nutrition, may not be referred to the stimulus of hope, permits of speculation.

Pituitary Body. As in the case of the glandular structures already considered, the function of the pituitary body is variously believed to be of a secretory or excretory nature.

Schaefer and Oliver's[32] experimental investigations with decoctions of its tissue indicate that its activity is of a secretory character.

Rapid and great rise of blood-pressure was observed, and it was shown that the action of the active principle was a direct one upon the arterioles and probably so upon the heart-muscles. They conclude from their results that the pituitary body furnishes a secretion to the blood which serves to increase the contractile power of the heart and arteries and to influence the nutrition of certain tissues.

On the other hand, very slight physiological effects, beyond a slight elevation of temperature, slight depression, and some gastro-intestinal disturbance accompanied by emaciation, were noted by Mairet and Bosc in their experimental work.[33]

Marie,[34] who first described the disease acromegaly, regarded by many as dependent upon pathological changes in the pituitary body, believes that the function of the gland is to neutralize or destroy certain toxins whose accumulation in the blood provokes a hyperplasia of connective tissue, including the bony structures.

On the basis of a presumable glandular activity, the use of preparations of the pituitary body has been suggested in acromegaly.

With few exceptions autopsies in cases of this disease have shown macroscopic lesions of the pituitary; they have consisted chiefly in simple hyperplasias of its structures or of tumors of various kinds with or without apparent change in the volume of its glandular tissue. Tamburini[35] has recently collected twenty-four autopsies in which tumor existed in seventeen, and of the remaining seven he considers the diagnosis of acromegaly to be doubtful in five. In the case of either lesion it is presumable that the function of the gland is affected. Both diminished secretion and hypersecretion have been suggested in explanation of the evolution of the symptoms of acromegaly. Clinical as well as pathological observations may be urged with equal force in favor or in disproof of either of these theories. From the standpoint of pathological anatomy, it may be said that while destructive lesions are the exception, they do occur; and in cases of tumor the absolute volume of the proper tissue of the gland, whether increased or diminished, affords no reliable indication of its functional activity. Experimental reduction of the volume of glandular tissue (Gley[36]) fails to support the theory of secretory failure.

Clinically, in a few cases the administration of pituitary extract has been found to relieve certain of the characteristic symptoms, a result which does not harmonize with the hypersecretion theory; and yet such a result is not necessarily incompatible with it. Still less does it negative the possibility of a hyperactivity of one element in a composite function, the product of which may not be present in the preparation as actually administered.

Marinesco has advanced the hypothesis that some perversion occurs in the composition of the secretion, or that some lack of balance arises between it and the products of the other ductless glands, as a result of which nervous control over the nutritive processes is impaired. In this way provision is made for including both the hypertrophic and the atrophic lesions of the gland.[37]

The idea of a correlated activity of several of the glands jointly influencing nutrition either directly or through the medium of the nervous system, is sufficiently elastic to cover almost any combination of circumstances; but it must be remembered that it is as yet an unproved hypothesis.

Arnold,[38] Dreschfeld,[39] and Dercum[40] go one step further and favor a primary nervous lesion of unknown character, thus reducing the glandular changes to phenomena of the second order.

In conclusion, it may be said that while the whole subject presents an accumulation of theories having an exceedingly slender support on definite findings, it is probable that the pituitary gland bears some unascertained relation to the nutrition of bony and dermal tissues, as a result of which an overgrowth of them accompanies changes in the gland which presumably affect its functions. Whether these changes are primary is as yet unknown.

A few cases have been reported which indicate a widespread involvement of the glands of internal secretion and suggest a possible common origin. Murray[41] has collected five cases of this kind; in all acromegaly and exophthalmic goitre coexisted, and in four glycosuria also was present, pointing, perhaps, to some perversion of the pancreatic secretion. In the two cases with fatal issue the thyroid and pituitary glands were enlarged, and in one of these the thymus was persistent and hypertrophied.

I have collected thirteen cases of acromegaly treated with pituitary preparations. In seven cases varying degrees of improvement were noted. In one of these the improvement occurred under the combined use of pituitary and thyroid preparations. In five cases no effect was obtained; and in one case the patient was made worse by the treatment.

In two cases of improvement the violent headache and neuralgic pains in the limbs were diminished, and the general condition otherwise improved. There was no diminution in the size of the affected tissues.

In a third case the general condition was improved; no painful symptoms had been present at any time.

In a fourth case, after fourteen days of treatment the patient was able to approximate the teeth better than before, and the patellar reflex on the left side, which had been absent, was restored. Under treatment with thyroid extract for several months previously no improvement had occurred.

In a fifth case it is stated that the patient had greatly improved under treatment.

In a sixth case the patient was treated for two months with thyroid preparations, then for three to four months with pituitary extract, and finally for one and one-half months with combined pituitary and thyroid preparations. The final result was a decided decrease in the measurements of the extremities, an almost complete disappearance of the neuralgic pains, and an improvement in the general condition.

Finally, in the seventh case, there was an improvement in the mental condition.

A tabulated report of these cases is appended.

ADRENAL PREPARATIONS IN ADDISON'S DISEASE.

Observer.	No. of cases.	Results.	Remarks.
Blackader, A. D., Montreal Med. Journ., Nov. 1893, and results from personal letter.	1	Distinct improvement.	Under treatment four weeks; energy and power of endurance greater; bronzing of skin less marked.
Chauffard, La Semaine Méd., 1894, p. 74.	1	Not improved.	
Abelous, Langlois, and Charrin, Arch. de Physiol., 1892, p. 721.	1	Not improved.	Patient profoundly tuberculous; death followed in a short time.
Sée (Germain), quoted by Abelous, Langlois & Charrin, Arch. de Physiol., 1892, p. 721.	1	Not improved.	Death shortly after from general tuberculosis.
Langlois, Bra. Methode Brown-Séquard, p. 536. Presse Méd., 1896, p. 1181.	1 1	Improvem't in asthenia. Not improved.	Passed out of observation at end of one month. Patient soon declined to be treated on account of pain at seat of the injections.
Lloyd-Jones, Brit. Med. Journ., 1895, ii. 483.	1	Improved.	
Francis, Brit. Med. Journ., 1896, i. 1088.	1	General improvement; cutaneous pigmentation lessened; pigment in mouth unchanged.	Improvement continued for several months, followed by relapse and death.
Dyson, Quart. Med. Journ., 1894, iii. 43.	1	Not improved.	Very advanced case.
Sansom, Brit. Med. Journ., 1895, ii. 1235.	1	Improved.	"Subjective symptoms improved wonderfully." Treatment was irregular, and at date of report patient was relapsing.
Althaus, Brit. Med. Journ., 1895, ii. 1235.	1	Improved.	Improvement only temporary, followed by death.
Stockton, Med. News, 1895, lxvii. 551.	1	Cured.	Pigmentation almost removed, and general condition practically restored to normal.
Murrell, Lond. Lancet, 1896, i. 289 (also Parkinson, Brit. Med. Journ., 1896, i. 150).	1	Not improved.	Asthenia and pigmentation three months; under treatment for the following six weeks, at the end of which death occurred.
Shoemaker, Univ. Med. Mag., Feb. 1895, p. 309.	1	Improved.	Subcutaneous injections of glycerin extract for two months. Subjective symptoms restored to normal, pigmentation about as before.
Turney, Brit. Med. Journ., 1896, i. 150.	2	Not improved.	Very advanced cases. One patient lived only two days; the other only two weeks.
Oliver (Thomas), Internat. Clinic, 1894, ii. 23.	1	Not improved.	
Ringer and Phear. Clin. Soc. Trans., xxix. 68.	1	Improved.	Asthenia and pigmentation improved until the end of the fourth week, when the appetite failed, and treatment was suspended. The patient died two weeks later.

Observer.	No. of cases.	Results.	Remarks.
Tonoli, Gaz. Med. Lomb., xlv. 321.	1	Cured.	Treatment with powdered adrenal tissue for two months.
Shattuck, report by Cabot, Med. News, 1896, lxix. 281.	1	Apparently well.	Has remained apparently well for four months.
Stewart (T. G.), rep. by Duckworth, 20th Cent. Pract., ii. 24.	1	Not improved.	
Spillmann, Rev. Méd. d.l'Est., 1896, xxviii. 44. Rev. des Sci. Méd., 1896, xlviii. 86.	3	2 not improved. 1 improved.	 Subsequently relapsed.
Osler, Internat. Med. Mag., Feb. 1896. Johns Hopkins Bul., 1896, p. 208.	1	Markedly improved.	Gained weight, strength fully restored, pigment has disappeared from palate, but not changed on integument. Eight months after the original report the patient, who has meanwhile been treated without much regularity, is said to be failing rapidly.
	1	Not improved.	Died on the seventh day of treatment.
Oliver (George), Brit. Med. Journ., 1895, ii. 561, 653.	1	Practically well.	Last report at end of twelve months' treatment. This case also reported by Rolleston and by Oliver several times.
	2	Markedly benefited.	One still under treatment at last note, the other lost sight of.
Wood, Univ. Med. Mag., viii. 483.	1	Apparently well.	Immediate improvement in subjective symptoms, after a few months apparently well; bronzing not affected.
	(2 or 3)	(Improvement.)	(Author states that he knows of these cases; no details.)
Stockman, Edin. Med. Journ., Feb. 1897, p. 211.	2	1 no improvement. 1 improved.	 Improvement had lasted twenty months at date of report. Patient is able to follow his ordinary occupation, but relapses occur when treatment is suspended.
Maragliano, Riforma Med., 1894, iv. 650.	1	Improvement.	Subjective improvement and increase in muscular strength. Able to walk after the tenth injection (twenty days), although previously bed-ridden.
Pitrés, Cong. de Méd. Int. Bordeaux, 1895.	2	Worse.	Injections caused severe local irritation and aggravation of symptoms.
Faisans, personal com. to Dupaigne, Thèse de Paris, 1896.	1	Improved.	Pigmentation improved, other symptoms persisted.
Dupaigne, Thèse de Paris, 1896, pp. 109, 118.	2	1 no improvement. 1 improved markedly.	An advanced tuberculous case. Improvement in pigmentation and asthenia while under treatment during three months. Died quite suddenly when treatment was suspended.
Epelbaum, Thèse de Paris, 1895.	2	1 improved.	Under treatment only a short time, and subsequently lost sight of: improvement very marked from two weeks' treatment.
		1 improved.	After two months of treatment was able to return to work.
Dieulafoy, Dupaigne, Thèse de Paris, 1896, p. 131.	1	Improved.	Improved only while under treatment; relapsed promptly each time it was suspended.
Bèclère, Dupaigne, Thèse de Paris, 1896, p. 133.	1	Cure.	Treated with ingestion of fresh gland for one month, and then for three and a half months with subcutaneous injections of extract. Pigmentation disappeared and patient was able to work. Cure had continued one year and a half at date of report, patient remaining under observation.

Observer.	No. of cases.	Results.	Remarks.
Marie, Dupaigne, Thèse de Paris, 1896, p.136.	1	Improved.	Asthenia less marked.
Bramwell, Brit. Med. Journ., 1897, i. 67.	1	Marked improvement.	Improvement lasted for a year, when death occurred. Asthenia improved so that patient shortly before his death was able to walk eight miles.
Quine, Journ. Amer. Med. Ass., 1896, xxvi. 1012.	1	No improvement.	Treatment only continued twelve days; patient died four days later.
Darier, Ann. de Derm. et d. Syph., 1895, p. 464. See also for termination, Dupaigne, loc. cit. p. 102.	1	No change.	Treatment suspended on fifteenth day on account of local abscess. He died soon after.
Schilling, Münch. med. Woch., 1897, p. 170.	1	Improved.	Three months' treatment; weight rose from 69-99 lbs. Strength fully restored, bronzing markedly diminished. Died three months later with toxæmic symptoms.
Kinnicutt (unpublished case).	1	No effect.	Treatment initiated only with the development of toxic symptoms. Death five days later. Diagnosis confirmed by autopsy: general tuberculosis, tuberculous and fibroid changes in adrenals.

THYMUS THERAPY IN EXOPHTHALMIC GOITRE.

Observer.	No. of cases.	Results.
Owen (Brit. Med. Journ., 1896, vol. ii. p. 1017)	3	Improved.
Williams (Clinical Journ., vol. vii. p. 93)	1	Worse.
Cunningham (Med. Record, vol. xlvii. p. 742)	3	Improved.
Taly-Guerin (Sem. Méd., 1895, p. 331)	1	Not improved.
Solis-Cohen (Philadelphia Polyclinic, 1896, vol. v. p. 446)	4	Improved.
Dreschfeld (Practitioner, 1896, vol. lvii. p. 154)	3	Not improved.
Todd (Brit. Med. Journ., 1896, vol. ii. p. 195)	1	Improved.
Maude (Lancet, 1896, vol. ii. p. 173)	4	Improved.
McKee (Brti. Med. Journ., 1896, vol. i. p. 656)	1	Improved.
Edes (Boston Med and Surg. Journ., 1896, vol. cxxxiv. p. 82)	1	Improved.
Mikulicz (Centrbl. f. Chir., 1896, p. 929)	8	1 improved. 7 not improved.
Parker (Brit. Med. Journ., 1897, vol. i. p. 528)	1	Improved.
Lockie (Brit. Med. Journ., 1897, vol. i. p. 529)	2	Improved.
Sutcliff (Brit. Med. Journ., 1897, vol. i. p. 782)	1	Improved.
Metcalf (rep. by Mackenzie, AMER. JOURN. MED. SCI., 1897, 132)	2	Improved.
Mackenzie (AMER. JOURN. MED. SCI., 1897, p. 132)	20	13 improved. 7 not improved.
Booth, J. A. (personal communication)	4	Not improved.
Kinnicutt	2	Not improved.

PITUITARY TREATMENT OF ACROMEGALY.

Observer.	No. of cases.	Results.	Remarks.
Bard, Lyon Méd., 1892, lxix. 547.	1	No result.	Pituitary extract from rabbit used subcutaneously. Author proposed to continue the treatment with extract derived from ox and sheep, but no further report can be found.
Marinesco, Bull. et Mém. Soc. Méd. des Hôp., 1895, p. 715.	2	Very much improved.	The violent headache and neuralgic pains in the limbs considerably reduced, and the general condition otherwise rendered more satisfactory. No diminution in size of diseased parts. Marked diuresis. Author believes that the treatment exercised an effect either on the pituitary tumor or the cerebral circulation.
	1	Slight improvement.	General condition improved. This patient did not present any painful symptoms.
Mendel, Berl. klin. Woch., 1895, 1129.	1	Improved.	After fourteen days' treatment patient was able to approximate the teeth better than before, and the patellar reflex on the left side, which had been absent, was restored. This case had been treated for several months with thyroid extract without improvement.
Bramwell, Brit. Med. Journ., 1894, i. 21.	1	Improved greatly.	Author states that improvement may have been due to favorable general conditions during hospital residence. Previous treatment with thyroid had failed in this case.
	1	No effect.	Subsequently improved under thyroid.
Thomas, Brit. Med. Journ., 1896, i. 909.	1	No effect.	Refused to continue treatment because it made her "feel queer." Subsequently relieved by trephining.
Dinke, N. Y. Med. Record, 1896, l. 779	1	Marked improvement.	Treatment for two months with thyroid, then for three to four months with pituitary, and finally for one month and a half with thyroid and pituitary combined. The final result was a decided decrease in the measurements of the extremities; pains had almost disappeared, and the general condition was improved. Patient believes that the improvement was due to the thyroid.
Osler, Prin. and Pract. of Med., (1895) p. 1047.	1	Not improved.	
Broadbent, Dodgeson, Lancet, 1896, i. 846.	1	Some improvement.	Chiefly in the mental condition; possibly due to the relief of the obstinate constipation.
Rolleston, Lancet, 1896, i. 1137.	1	No improvement.	Measurements increased. Author attributes the relief in pains and diminution of glycosuria to rest and diet.
Schultze, Berl. klin. Woch., 1896, p. 407.	1	Worse.	Caused irregularity of heart-action, and death followed.

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AN ANATOMICAL AND BACTERIOLOGICAL STUDY OF ACUTE DIFFUSE NEPHRITIS.

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The kidney is a glandular organ, but there is no gland in the body with which it may be compared. The peculiarity in the structure of the kidney lies in its blood-supply and in its structure as a gland. There is in the kidney a structure corresponding to a gland, and leading from this an excretory duct which also has true glandular properties of its own, so that the kidney may be considered as a double glandular organ. The glomeruli have the structure of true glands, with capillary wall, basement-membrane, and differentiated epithelium. The tubule leading from the glomerulus may be considered partly as an excretory duct for that glandular structure, but it has glandular functions of its own as well, and adds various substances to the secretions of the glomerulus. The circulation of the kidney is peculiar in that nearly all of the blood passes first to the glomerulus, and after circulating in the capillaries of this leaves the glomerulus in a single vessel, which again breaks